COMPOSITIONS FOR CANCER THERAPY SAPONINS OR SAPOGENINS

FIELD OF THE INVENTION

The present invention pertains to the field of cancer therapy and in particular to compositions comprising saponins and/or sapogenins for use in the treatment of cancer.

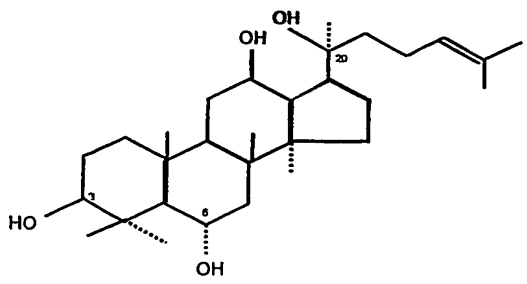
BACKGROUND

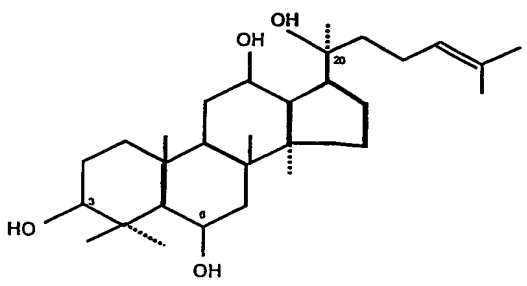
There is a continuing need for development of new anti-cancer drugs and drug combinations. Accordingly, cancer research has been increasingly directed to the discovery of novel anti-cancer agents obtained from natural sources, as well as identifying and preparing synthetic compounds found in these natural sources.

Ginseng has long been recognized as a general tonic and a benign and safe herb. Many of the components of ginseng have been isolated and have been classified as: ginsenosides, carbohydrates, nitrogenous compounds, fat-soluble compounds, vitamins and minerals. The saponins derived from ginseng (also called "ginsenosides") are believed to be the main active components of ginseng.

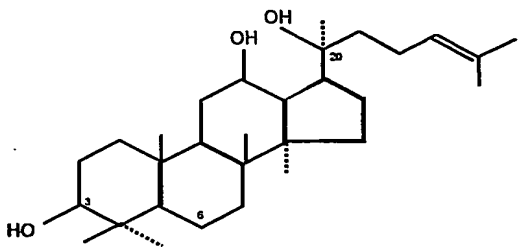
Saponins, in general, are composed of a sugar portion (glycon) and a non-sugar portion (aglycon or sapogenin). The sapogenins in ginseng, the backbone of saponins, are further classified into three types: protopanaxadiol and protopanaxatriol (which are tetracyclic terpenoids of the dammarane series), and oleanoic acid.

The sapogenin aglycon protopanaxatriol (aPPT) has the following chemical structures:



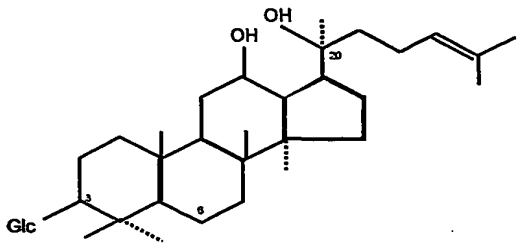


The sapogenin aglycon protopanaxadiol (aPPD) has the following chemical structure:



More than 25 dammarane-type saponins have been isolated from Panax ginseng C.A. Meyer, which vary in the number and type of monosaccharide residues present in the sugar side chains. The individual ginsenosides are named Rx according to their mobility on thin-layer chromatography plates. Examples of known ginsenosides include those in groups Ra through Rh. The isolation of three new dammarane-type saponins (named Rk1 to Rk3) from heat-processed ginseng has also been reported recently (see Park, I.H. (2002) Arch Pharm Res. 25: 428-32).

In recent years, the beneficial effects of ginsenosides in the treatment of cancer has been reported. For example, U.S. Patent Application Nos. 09/910,887 (published as: 20030087835) and 09/982,018 (published as: 20030087836) describe novel sapogenin compounds having anti-cancer activities. Similarly, U.S. Patent No. 5,776,460, reports ginsenoside Rh2 [3-O-β-D-glucopyranosyl-20(s)- protopanaxadiol] to have anti-cancer activities. Rh_2 is a saponin having the following chemical structure, in which "Glc" is the glycon (glucose):



The literature also shows that Rh2 can induce differentiation and apoptosis of cancer cells (Kikuchi Y. et al. (1991) Anti-cancer Drugs. 2: 63-7; Lee KY et al. (1996)

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A composition comprising an activity-enhancing amount of two or more saponins, two or more sapogenins, or one or more saponins in combination with one or more sapogenins, and having anti-cancer activity.

2. The composition according to claim 1, wherein the saponins and sapogenins are selected from the group comprising: Rh2, aglycon protopanaxatriol, and aglycon protopanaxadiol.

3. The composition according to claim 2, comprising between about 1-90% each of Rh2, aglycon protopanaxatriol, and aglycon protopanaxadiol.

4. The composition according to claim 3, comprising between about 1-50% of Rh2, between about 5-40% of aglycon protopanaxatrioland between about 5-75% of aglycon protopanaxadiol

5. The composition according to claim 4, comprising between about 5-40% of Rh2between about 5-40% of aglycon protopanaxatriol, and between about 10-70% of aglycon protopanaxadiol.

6. The composition according to claim 1, wherein one or more of said saponins and sapogenins are extracted from plant material.

7. The composition according to claim 6, wherein said plant material is derived from one or more plants from the genus *Panax*.

8. The composition according to claim 7, wherein said plant is *Panax ginseng*.

9. The composition according to claim 7, wherein said plant is *Panax quinquefolium*.

10. The composition according to claim 7, wherein said plant is *Panax notoginseng*.

11. The composition according to claim 1, wherein one or more of said saponins and sapogenins are synthetic.

12. A pharmaceutical formulation for the treatment of cancer, comprising a therapeutically effective amount of the composition according to claim 1 and a pharmacologically acceptable carrier.

13. A non-pharmaceutical formulation for the treatment of cancer, comprising a therapeutically effective amount of the composition according to claim 1 and a pharmacologically acceptable carrier.

14. The formulation according to claim 12 or 13, wherein the formulation is in an orally administrable form.

15. The formulation according to claim 12 or 13, wherein the formulation is in an injectable form.

16. The formulation according to claim 12 or 13, wherein the formulation is in a topically applicable form.

17. The formulation according to claim 12 or 13, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000mg of Rh2 per kg bodyweight per day.

18. The formulation according to claim 12 or 13, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000mg of aglycon protopanaxatriol per kg bodyweight per day.

19. The formulation according to claim 12 or 13, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000mg of aglycon protopanaxadiol per kg bodyweight per day.

20. Use of the composition according to claim 1 for the treatment of cancer in a mammal.

21. The use according to claim 20, wherein said cancer is selected from the group consisting of glioma tumor, melanoma, breast cancer, pancreatic cancer, brain tumor, intestinal and gastric cancers, prostate cancer, and lung cancer.

22. The use according to claim 20, wherein said cancer is selected from the group consisting of stomach cancer, esophagus cancer, colon and rectum cancer, ovary cancer, liver cancer, kidney cancer, larynx cancer, bone cancer, multiple myeloma, bladder cancer, cancer in body of uterus, oral cavity cancer, thyroid cancer, cervix cancer, testis cancer, non-Hodgkin's lymphoma, leukemia, Hodgkin's disease, skin cancer, and soft tissue cancer.

23. The use according to claim 20, wherein said cancer is a multi-drug resistant cancer.

24. The use according to claim 23, wherein said multi-drug resistant cancer is a primary cancer selected from the group consisting of cancers of muscle, bone or connective tissues, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive tract, pancreas and thyroid or adrenal glands, including solid tumors, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangioma, chorioma, neuroblastoma, Wilms' tumor, Hodgkin's disease, melanomas, multiple myelomas, lymphatic leukemias and acute or chronic granulocytic lymphomas.

25. The use according to claim 23, wherein said multi-drug resistant cancer is a recurrent cancer selected from the group consisting of pancreatic cancer, lung cancer, stomach cancer, esophagus cancer, colon and rectum cancer, brain cancer, ovary cancer, liver cancer, kidney cancer, larynx cancer, bone cancer, multiple myeloma, melanoma, breast cancer, prostate cancer, bladder cancer, cancer in

body of uterus, oral cavity cancer, thyroid cancer, cervix cancer, testis cancer, non-Hodgkin's lymphoma, leukemia, Hodgkin's disease, skin cancer, and soft tissue cancer.

26. The use according to any one of claims 20-25, wherein said composition is used in combination with one or more other chemotherapeutic agents.

27. The use according to any one of claims 20-25, wherein said mammal is a human.

28. The use of a composition according to claim 1 in the manufacture of a medicament for the treatment of cancer.

29. A pharmaceutical kit for the treatment of cancer in a mammal comprising the composition according to claim 1 and one or more containers.

Figure 5 Efficacy of minimum concentration of the Invention on various cancer cells

Cancer cell lines	Cancer Type	Minimum concentrations for 100% cell killing	
MCF7/adr	Breast cancer	40 ug/ml	Drug resistant
MDA435LCC6M	Breast cancer	40 ug/ml	Drug resistant
MCF-7/c3	Breast cancer	40 ug/ml	Caspase-3 positive
9L	Brain tumor	25 ug/ml	
SF188	Brain tumor	20ug/ml	
LNCaP	Prostate tumor	25 ug/ml	
PC3	Prostate tumor	40 ug/ml	
HCT15	Intestinal & Gastric tumor	40 ug/ml	
Keto	Intestinal & gastric tumor	35 ug/ml	
H460	Lung cancer	40 ug/ml	